REMARKS

Claims 51-61 remain under active prosecution in the present application. Claims 37-50 and 62-65 are withdrawn as being drawn to a non-elected invention. Claims 1-36 have been previously canceled. Claims 51, 53-61 are currently amended. Applicants respectfully submit that all amendments are supported by the original disclosure and do not introduce new matter. Specifically, support can be found in paragraphs 0042, 0045 and 0048.

By way of review, the pending claims relate to methods of providing biologically active lipid hydrolyzing proteins or polypeptides to cells of a mammal comprising administering into cells a vector that comprises a DNA sequence encoding the lipid hydrolyzing protein. One such lipid hydrolyzing protein that may be used with the claimed methods is lysosomal acid lipase (LAL). Such proteins are useful for the treatment and prevention of atherosclerosis.

In the subject Office Action dated November 21, 2007, the Office has rejected claims 51-61 under 35 U.S.C. §112, first and second paragraph. Applicants' arguments in response to these rejections are set forth below.

Claim Rejection - 35 USC § 112, second paragraph

Applicants appreciate the Examiner's withdrawal of the rejection of claim 54 under 35 U.S.C. 112, second paragraph, as being the result of a typographic error.

The Examiner has maintained the rejection of claim 55 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner contends that there is no polypeptide sequence of any lysosomal acid lipase disclosed in the specification and that the phrase "substitution of amino acid Pro (-6) to Thr and Gly2 to Arg" recited in claim 55 of instant application is vague and indefinite.

Applicant have now amended the claims to provide for a method for providing biologically active lysosomal acid lipase-to cells, said method comprising administration into cells a vector comprising and expressing a DNA sequence encoding biologically active lysosomal acid lipase, and expressing the DNA sequence in said cells to produce biologically active lysosomal acid lipase capable of hydrolyzing lipids. As previously stated, with respect to the lysosomal acid lipase, both the amino acid and DNA sequence were published and well

known in the art at the time of filing. In particular, Ameis et al., *Eur. J. Biochem.* 1994, reference cited by applicants at paragraph [0037] discloses the cDNA and peptide sequence sufficient to enable the instant invention. As such, applicants' assert that the claim is not vague or indefinite, and the rejection to the claim should be withdrawn.

The Examiner has newly rejected claims 51-55 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amended claim 51 recites the limitation "the sequence" in the phrase "wherein the sequence contains the catalytic lipase triad Asp-Ser-His". The Examiner contends that there is insufficient antecedent basis for this limitation in the claim. The claim has now been amended to remove this limitation.

The Examiner contends that claim 54 is unclear with respect to the newly added limitation "showing biological activity *similar to* that of lysosomal acid lipase." The claim has now been amended to remove this limitation.

Claim Rejection - 35 USC § 112, first paragraph

The Examiner has maintained the rejection of claims 51-61 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With regard to the claim rejection directed towards *lipid hydrolyzing protein or polypeptide acid lipases* (claims 51- 55) as lacking sufficient structure that would provide any reliable information about the structure of other lysosomal acid lipase DNAs, Applicant have now amended the claims to remove this limitation.

With regard to the claim rejection directed towards *lysosomal acid lipases* (claims 56-61), Applicant have now amended the claims to remove this limitation.

With regard to the claim rejection directed towards *lysosomal acid lipases* (LAL, claims 56- 61), the Examiner is placing her subjective view of the art into the description. In the present claims, the level of skill in the art is such that knowledge of conserved regions in a protein allows

one to predict the general structure of operable variants such that every variant need not be disclosed given only those sequences operable to produce a biologically active lysosomal acid lipase that is capable of hydrolyzing lipids will fall within the scope of the invention. Such sequences are well within the routine laboratory testing procedures for assaying enzymatic activity. It is not pertinent that some variants may show reduced, even significantly reduced, enzyme activity compared to wild-type LAL. Those mutants with reduced activity still present a workable invention. There is no requirement that a patent only claim optimal activity

Furthermore, there is no requirement that the specification disclose any nucleotide sequence that encodes a lysosomal acid lipase from mammalian lipase DNAs or human lipase DNAs or other lysosomal acid lipase DNAs from other cell types as long as this information is well-known and readily available in the art..

In conclusion, the specification is described in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, Applicant had possession of the claimed invention recited as recited in the amended claims.

The Examiner has maintained the rejection of claims 51-61 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Applicant respectfully disagree and state emphatically that gene therapy techniques were well within the skill of the art at the time of filing, such that undue experimentation is not required. It is not a requirement that clinical trials be performed in order to obtain a patent. Furthermore, there is no patent rule that states that a claim may not be obtained simply because it may involve a method that is determined to be on the level with gene therapy. Gene therapy patents are routinely allowed and there is no evidence that the present invention lacks in any enablement.

Applicant have demonstrated that at the time of filing the level of skill in the art is high, and Applicant provides the following references regarding successful administration of genes to produce biologically active proteins:

> Rosengart, T, "Angiogenesis Gene Therapy: Phase I Assessment of Direct Intramyocardial Administration of an Adenovirus Vector Expressing VEGF 121 cDNA to Individuals with Clinically Significant Severe Coronary Artery Disease,"

Circulation 1999; 100:468-474, "Rosengart I"; and Rosengart, T., et al., "Six-Month Assessment of a Phase I Trial of Angiogenic Gene Therapy for the Treatment of Coronary Artery Disease Using Direct Intramyocardial Administration of an Adenovirus Vector Expressing the VEGF 121 cDNA," Annals of Surgery 1999; 230: 455-472, "Rosengart II."

Losordo, D.W., et al, "Gene Therapy for Myocardial Angiogenesis: Initial Clinical Results with Direct Myocardial Injection of phVEGF 165 as Sole Therapy for Myocardial Ischemia," Circulation 1998; 98:2800-2804. Shetty, K. et al, "Gene therapy of hepatic diseases: prospects for the new millennium," Gut 2000; 46:136-139

Hirschowitz, E., "Regional treatment of hepatic micrometastasis by adenovirus vector-mediated delivery of interleukin-1 and interleukin-12 cDNAs to the hepatic parenchyma," Cancer Gene Therapy 1999; 6:491-498.

Applicant have shown that in Rosengart I and II, both published in 1999, a recombinant adenovirus (Ad) gene transfer vector containing vascular endothelial growth factor (VEGF) cDNA was successfully administered directly to an ischemic area of the myocardium in patients with coronary artery disease, showing cardiovascular improvement both one and six months after treatment with the gene. Applicant also argues that Losordo et al. demonstrates successful gene transfer of DNA (encoding VEGF) to the myocardium, and Losordo showed no operative complications, and marked symptomatic improvement and/or objective evidence of improved myocardial perfusion in all patients. Applicant further show that Shetty et al. described successful methods of gene delivery to the liver, including retroviral vectors, adenoviral vectors, adeno-associated vectors, simian virus 40 vectors, and hybrid viruses. As a final example, Applicant argues that Hirschowitz et al. demonstrate successful use of adenovirus vector-mediated delivery of DNA sequences to produce high levels of corresponding protein in the liver.

With regard to the references pertaining to unpredictability of gene therapy cited by Examiner (Pouton et al., 2001; Johnson-Saliba et al., 2001, Read et al., 2005, Dobson et al., 2006), Applicant shows that in Read, et al., at p. 21, the authors indicates that administration of

DNA/lipid mixtures is safe and can produce clinically significant responses. Applicant further argues that in Read, et al., p.22, the authors indicate that hydrodynamic delivery to the liver via a superficial vein is referred to as the simplest successful in vivo delivery route, having few barriers to delivery.

In response, the Examiner notes that the key message of citing Pouton et al., 2001; Johnson-Saliba et al., 2001, Read et al., 2005, and Dobson et al., 2006 is to show that gene therapy is unpredictable and the enabling support of a given claimed gene therapy is evaluated on a case-by-case basis. The Examiner's interpretation of these cited references is that gene therapy is unpredictable and many factors need to be considered, including the characteristics of the gene and its product, the vector used for delivery, administration of the vector, targeting the gene to desired cells and cellular compartment, initiation and sustained expression of the gene, potential unexpected side effects associated with gene therapy, extrapolation from animal models to human beings etc.

Applicant's respectfully point out that the cited "unpredictable" elements cited above are not shown to be proof that the present method, as claimed, is unpredictable. In the present invention, the enzyme is used in a predictable fashion and delivered in a predictable delivery vehicle. There is no requirement that the product be delivered only to certain cells of that a certain level of expression be obtained. There is no requirement that any effective treatment is accomplished.

As noted by the Examiner, the evaluation of enabling support is done on the case-by-case basis. In the present case, the Examiner has not shown any reason why the present method is, in view of the state of the art, unpredictability in the art.

Claim Rejection - 35 USC § 102

Applicants appreciate Examiner's withdrawal of the rejection of claims 51-54, and 56-61 under 35 U.S.C. 102(e) as being anticipated by Xiao (Xiao, U.S. Patent Application Publication No: 2004/0038365, Publication date Feb. 26, 2004).

Applicants appreciate Examiner's withdrawal of the rejection of claims 51-54 and 56-61 35 U.S.C. 102(e) as being anticipated by Kapeller-Libermann (Kapeller-Libermann, U.S. Patent Publication No: 2002/0193303, Publication date, Dec 19, 2002).

Conclusion

In light of the amendments and remarks made herein, it is respectfully submitted that the claims currently pending in the present application are in form for allowance. Accordingly, reconsideration of those claims, as amended herein, is earnestly solicited. Applicants encourage the Examiner to contact their representative, Stephen R. Albainy-Jenei at (513) 651-6839 or salbainyjenei@fbtlaw.com.

The Commissioner for Patents is hereby authorized to charge any deficiency or credit any overpayment of fees to Frost Brown Todd LLC Deposit Account No. 06-2226.

Respectfully submitted,

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